1 Genetic Registers

- Genetic registers or health records contain data/information and not tissue - not described as "biobanks"
- ***But*** invaluable for linkage studies eg cancer studies

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2 Research Uses of Biobanks

- Large scale research and biobanks and rising health costs (cancer, diabetes, heart diseae).
- Large scale genetic epidemiology studies; Disease gene/proteomic discovery studies
- Pharmacogenomics - matching drug to individual patient (effectiveness and minimising ADRs)
- National biotechnology strategies("..safeguarding human health..environment..capture.. benefits of biotechnology for…community, industry and environment" (*Australian Biotechnology: A National Strategy*:2000).

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2 Uses of Biobanks

- "Biobanks are increasingly seen as an essential tool in translating biomedical research into real improvements in healthcare" (*Genetic Engineering News* , 2005 Vol 25 no3)
- Biobanks include collection and management of samples, governance of databases and commercialisation aspects.
- Convergence of technologies

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2 Uses of Biobanks- Technology

3 Growth of Biobanks: Local to Global

- DeCode (Iceland);Estonian Genome; Biobank (UK),
- Karolinska Institutet (Sweden); CARTaGENE (Quebec),
- GenomEUtwin (Finland); Danubian Biobank Foundation (six countries in Central Europe); KORA-GEN(Germany); LifeGene (Sweden); Generation Scotland
- INMEGEN (Mexico); LifeLines (Netherlands); National Heart, Lung and Blood Institute (NIH USA); Centre for Integrated Genomic Medical Research (UK).
- Australia: WA Genetic Health project (Busselton);Victoria cancer consortium;Tasmania Menzies Centre

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3 Biobanks: Local to Global

- *International Haplotype Mapping Project:* USA, UK, Japan, Nigeria China and Canada collaboration to identify/compare genetic similarities/differences to find genes that affect health, disease and medication responses
- *Public Population Project in Genomics* (P3G); not-for-profit public and accessible knowledge database for the international population genomics community, (motto - transparency and collaboration)

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4 Challenges of Biobanks

- Rand Corporation study about technical challenges from inconsistencies in the collection, storage and access policies of biobank
- Privacy (legislation) -access; release

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4 Challenges - Technical

- Decision on number of data points to be collected in relation to each individual sample and then the actual coding of the collected sample.
- Genetic information is "sensitive" and should be protected by encryption codes (Privacy Enhancement Technology -PETs) and only accessible to authorised biobank employees.
- Collection and testing facilities must comply with accreditation standards.
- Sample collection and storage must be quality assured and not tainted by human/process error.

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4 Challenges - Technical

GEN

Genetic Engineering & biotechnology News

Biotechnology from bench to business

Volume 28, Number 2 January 15, 2008

Centre for Law & Genetics

4 Challenges - Technical

Biobanking Needs More Standardized Procedures

Personalized Medicine Brings Unique Requirements for Managing Specimens

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4 Technical Improvements

- Industry standards for biobanks are developing,
- *First-Generation Guidelines for NCI-Supported BioRepositories* (National Cancer Institute, National Institutes of Health, U.S Dep Health /Human Services)
- *International Society for Biological and Environmental Repositories* (ISBER).

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4 Challenges- Ethical/legal

- Research misuse eg inappropriate transfer of tissue or new *unconsented* use
- Inappropriate waivers of consent for existing collections
- Commercialisation
- Role of Research Ethics Committees
- Data Linkage
- Public Trust

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5 Ethical principles for Biobanks

1 Proper Research Governance governance structures appropriate for primary research focus and protection of the interests of the research participants.

- UK Biobank, *Ethics and Governance Framework*, Version 2.0
- OECD,*Creation and Governance of Human Genetic Research Databases* (2007)
- Transnational Recognition of Research Ethics Approvals

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5 Ethical principles for Biobanks

2 Transparency

- Public trust and accountability.
- Public engagement a major feature of the development of major public biobanks (See OECD (2007) particularly Chapter 3.5 *Public Engagement in the Establishment of a Population Database).*
- Public Consultation in development of national guidelines and institutional policies (eg Human Genetics Advisory Committee, Australia).

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5 Ethical principles for Biobanks

3 Independent Control of Data and Samples

- Best practice for an independent intermediary between the researcher and the data/samples
- *Steward, custodian, charitable trustee.*

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5 Ethical principles for Biobanks

4 Consent: Future biobank projects - re-contacting participants for new information, new uses, or new research).

- a) *Limited /specific consent* for research for use of biospecimen for a specific project, or
- b) *Qualified/follow-up* consent where participant wishes to be contacted in future if there is any extension or substantial variation from original research project, or
- c) *Full/unspecified* consent to use of biospecimens in all future research ("blanket' consent)

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5 Ethical principles for Biobanks

5 Consent: Existing tissue collections

Research Ethics Committee may *waive* consent to use existing collections for *secondary* research purposes, after considering

- existing consents; whether difficult or intrusive to obtain specific consent; whether the research an extension of a previously approved project justification for the research
- arrangements to protect privacy
- whether a risk to the privacy/well being of participant;
- possibility of commercial exploitation of the sample;
- most importantly, whether the public interest in the value of the research *outweighs* the requirements of personal privacy.

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5 Ethical principles for Biobanks

6 Privacy and Confidentiality

- *Privacy legislation* information should generally be relevant to the purpose for which it is collected.
- Data Protection

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5 Ethical principles for Biobanks

7 Guidelines

- National codes,
- Special ethics frameworks eg UK *Biobank Ethics and Governance Framework* and *First-Generation Guidelines for NCI-Supported BioRepositories* National Cancer Institute, National Institutes of Health, U.S Department of Health and Human Services

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5 Ethical principles for Biobanks

8 Anonymysation *How anonymous - myth of de-identification?*.

9 Tracking Data Access and Exchange Proper records of access to and release of information, including licences or materials transfer agreements (MTAs).

10 Health Related Information Policy required on whether to reveal health information to participants at recruitment.

11 Withdrawal from project Right to withdraw at different levels, (complete withdrawal and destruction of samples; allow use of sample but not participating in any way; retention of sample with withdrawal from future projects).

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5 Ethical principles for Biobanks

12 Benefit Sharing -equitable distribution of benefits from research (Research and health care products?)

13 Closure and Termination of Biobank clear guidelines on transfer, closure of assets

14 International harmonisation of guidelines and advisory statement

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Conclusions

- Research ethics guidelines -OECD Creation and Governance of Human Genetic Research Databases (2007)
  - Transparency and public trust
  - Privacy/data security legislation
  - Harmonisation internationally
  - Children?
  - The need for a "chain of responsibility" (German/French Declaration)

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Taiwan Biobank & Ethical Regulations

FAN, Chien Te
Professor of Law, National Tsing Hua University
Director, Bioethics & Law Center, NTHU
2008/3/22

1

Special Features of Taiwan Biobank

1. The participants will be recruited on the voluntary basis.
2. There are three collection sites evenly allocated in northern, southern and eastern Taiwan.
3. The participants are people of the age between 30 with no gender restriction.
4. People of foreign nationality, foreign ancestry and/or diagnosed with cancer are excluded.
5. Collected samples include venous blood of 33 ml and urine of 15 ml
6. Other data to be collected include the health condition, history of diseases, lifestyles of the participants, and the personalized information about their living environment as well as samples of the environment.
7. The health condition of the participants will be retrieved for a longer period of time, so that researchers can embark on examining the interaction between gene and environment (including life habit, food, behavior and occupation etc) for the cause of common chronic diseases, which is beneficial to the further study in finding the solutions to improve the condition of preventing, diagnosing and treating these diseases.

2

ELSI & Public Trust Building

5

- Till now, the ELSI issues remain the most difficult part of the research. While, it's been always burdensome to develop an accountable ELSI governance framework within 1-2 years, the long lacking of trust between researcher and subject and/or physician and patient in Taiwan have even more seriously deteriorated the slim public trust. In the past one and a half year, the project has been mistakenly challenged for unethical practices several times. However, all the accusations were, in fact, nothing to do with this project.
- So far, the Ethical Governance Framework of Taiwan Biobank has been reviewed and officially notified. The draft bill of Taiwan Biobank Act has been submitted to the DOH for approval, too. In additions, the Feasibility Study also indicated to us a good tendency of participant's support in the exist survey. However, the public communication which may enable the public trust and a workable consent mechanism that may harmonize the respect of individual autonomy and the need to pursue variable and uncertain future applications remains wanting.

6

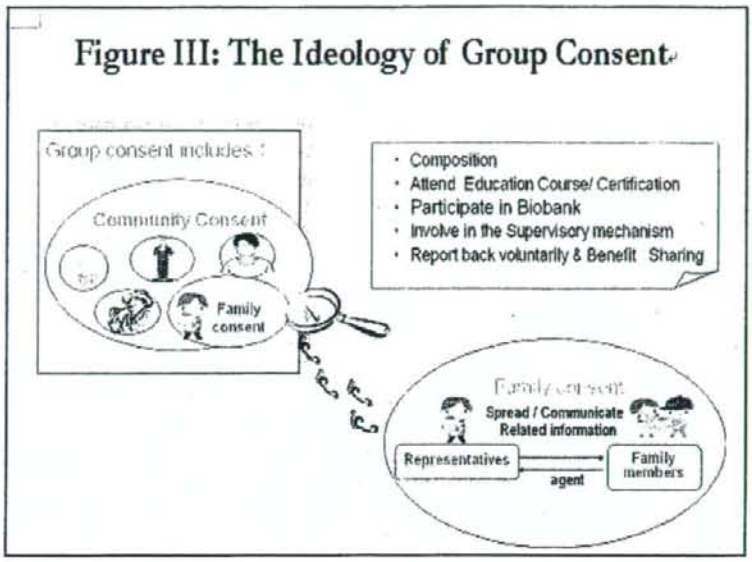


Figure III: The Ideology of Group Consent
Group consent includes :
Community Consent
Family consent
· Composition
· Attend Education Course/ Certification
· Participate in Biobank
· Involve in the Supervisory mechanism
· Report back voluntarily & Benefit Sharing
Family consent
Spread / Communicate Related information
Representatives
agent
Family members

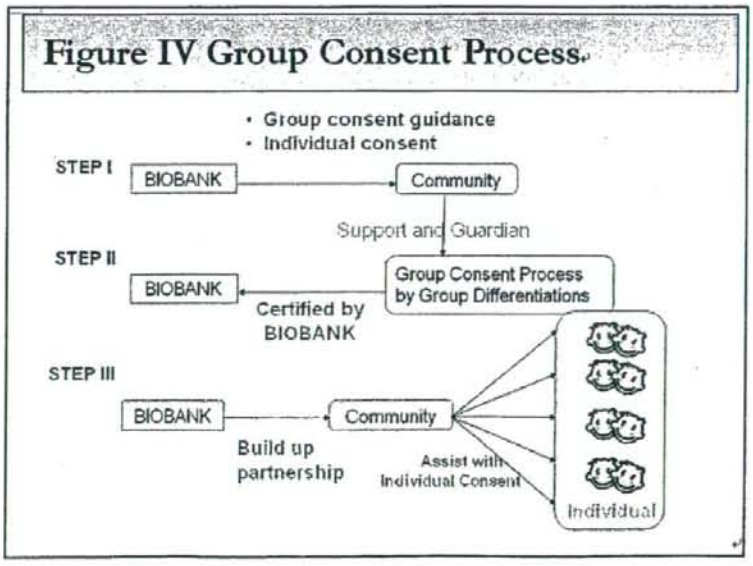
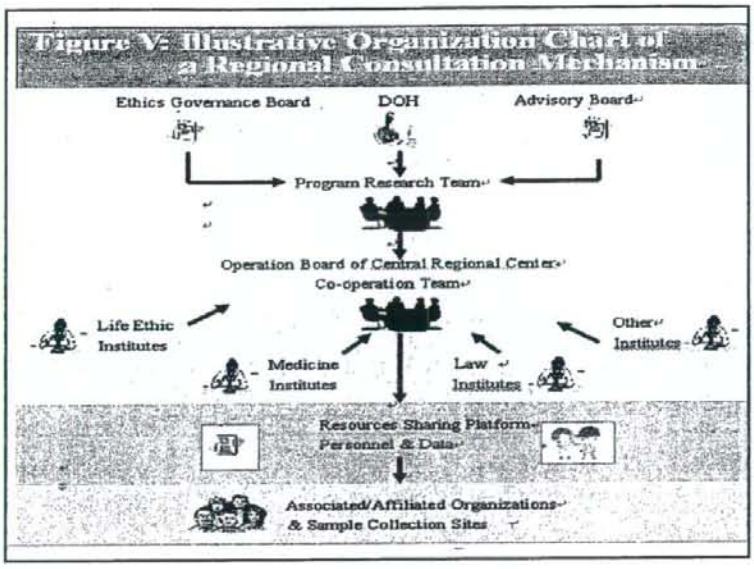


Figure IV Group Consent Process
· Group consent guidance
· Individual consent
STEP I
BIOBANK
Community
Support and Guardian
STEP II
BIOBANK
Group Consent Process by Group Differentiations
Certified by BIOBANK
STEP III
BIOBANK
Community
Build up partnership
Assist with Individual Consent
Individual



Core Issue III:
Aboriginal People's Participation

14

Taiwan Biobank: a project aiming to aid Taiwan's transition into a biomedical island

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Essentially, the term 'biobank' can be defined in different ways. Taking the UK Biobank's experience as the main example, the Taiwan Biobank aims to collect the DNA of a large group of people on the population base and track their health and lifestyle for at least 10 years. It is hoped that the information collected, regarding the mechanisms underlying how genes and environmental factors interact with each other to make us ill, will benefit the society in variable ways, including the exploration of a new generation of treatments, support to preventive medicine discovery and also the possible benefits for the promotion of evolving public health-related industries in Taiwan. However, the involvement of large-scale population base gene data collection also triggered serious ethical, legal and social issues. In Taiwan, the challenge is even more serious than for any other biobanking experiences that have occurred previously. Among all the ethical, legal and social issues, the convergence of aboriginal people protection provided under Taiwan's Constitution imposes on the research team an obligation to create an innovative Ethical & Legal Governance Framework adaptable to the unique social background of Taiwan, including a workable public consultation/communication mechanism. In early 2005, the creation of the 'Taiwan Biobank' has been included as a part of Taiwan's strategic development in promoting the country as an island of biomedicine. In this report, the ideology, the goals and special features, government strategy, visions and, in particular, the ethical, legal and social issue planning of the Taiwan Biobank will be briefly introduced and reviewed.

Keywords: biobank, DNA, ELSI, gene, gene database, gene medicine, genomic research, informed consent, medical record, pharmacogenomics, Taiwan

future medicine part of fsg

Envisioning the arrival of the gene era and opportunities derived from the fast bioinformatic technology development, Taiwan, with its profound genomic medicine and clinical research experiences in hand, has decided to invest a significant amount of resources in population-wide gene database development so as to enhance the capacity, through the further analysis of molecular-level population-based genetic information, in translating the interactions among genes, life phenomena, disease mechanism and environmental factors, and to benefit the biomedicine research and medicare solution also.

Since eraly 2005, Taiwan has initiated a daring national project to promote Taiwan as an island of biomedicine technologies. It aims to promote Taiwan as an Asian genomic medicine research and clinical trial center and to pursue the goal in developing an 'Island of Biomedical Science and Technology' of excellence. The project is composed of three major plans, including the 'Taiwan Biobank', the 'National Health Information Infrastructure' and 'Contract Research Organization'.

It has been the policy maker's vision that the Taiwan Biobank, together with the National Health Information Infrastructure, will make the convergence of biological information and medical records possible, so as to strengthen Taiwan's capacity in gene medicine research. Further backed up with the profound clinical Contract Research Organization rendering system in translational medicine, Taiwan is able to raise its global competitiveness in biomedical research, to earn a chance to ease the high cost of a national health insurance program, and to develop its biomedical research and healthcare industries.

Meanwhile, the Taiwan Biobank, just like other similar international approaches, can not ignore the possible ethical, legal and social issues (ELSIs) [1].

First, it is the tremendous amount of public resources appropriated for the plan that make the observation of democratic rules fundamental. Second, the ethical norms shall be taken as the premise in order to earn the required public trust. Third, the unique features of the population-wide involvement, especially of the aboriginal people, also complicates the public image of this development, which makes further social anthropological discovery necessary. This is particularly true in relation to the performance of informed consent obligation, when most of the

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stakeholders do not really understand the context to be consented for. Therefore, the best way in which to promote an effective/efficient public communication and find a balance between the protection of human dignity and the pursuit of scientific welfare vision is one of the most challenging issues for the Taiwan Biobank.

In comparison with some western country's profound experiences in ethical code observation in relation to medicine-related research, it is undeniable that Taiwan has long been questioned by domestic human right groups for a lack of sufficient public trust in conducting human-related research. Besides, whether or not a newly emerging western-style democratic society like Taiwan is mature enough to handle such a sophisticated plan of variable and/or conflicting social values is, indeed, a case to be explored.

So far, a Feasibility Study embarked since early 2006 has been concluded [101]. A further four-year Pilot Research Plan was initiated in the same year. It is expected that a comprehensive study delivered by the plan will provide Taiwan with a solid foundation for its biobank development [102].

Features & aims of the program

The Taiwan Biobank will collect, store and analyze the biological data necessary for the research designed to trace the common chronic diseases occurring locally in Taiwan; including high blood pressure, diabetes, cancer and other chronic diseases that may happen in the future anywhere other than Taiwan. From the scientific perspective, the main purpose of the Taiwan Biobank establishment is to meet the design requirement of traceable researches. Some of the program features are:

- Participants will be recruited on a voluntary basis;
- There are three collection sites evenly allocated in northern, southern and eastern Taiwan;
- Participants are people aged approxiamtely 30 years with no gender restriction;
- People of foreign nationality, foreign ancestry and/or diagnosed with cancer are excluded;
- Collected samples include venous blood of 33 ml and urine of 15 ml;
- Other data to be collected include the health condition, history of disease, lifestyles of the participants and the personalized information regarding their living environment as well as samples of the environment;
- The health condition of the participants will be retrieved for a longer period of time so that researchers can embark on examining the interaction between genes and environmental factors (including life habit, food, behavior and occupation and so on) for the cause of common chronic diseases, which is beneficial to the further study in finding the solutions to improve the condition of preventing, diagnosing and treating these diseases.

Given the unique features of risk factor profiles and the genetic background of the Taiwanese people, it was thought to be highly beneficial for Taiwan to own a biobank that was specifically designed for Taiwanese population, as it would enable large-scale cohort studies to be carried out for common diseases locally occurring in Taiwan. In regard to the scientific values, the program was thought to be beneficial as listed here:

- The genetic background of the Taiwanese population, in comparison with most of the white race, tends to be homogenous by character [2], mainly in composition of Ho-ló [103], Hakka [104] and aboriginal peoples, who will benefit the associated studies in terms of fewer population stratification limitations, which may yield certain advantages for studying the effects of subtle genetic variations, such as genotypic polymorphisms Besides, the Taiwanese people have been a homogenous people, with the significance of linkage disequilibrium (LD) weaker, which will benefit the exploration of gene's correlation with disease and the targeting [3].
- The people in Taiwan live mainly in western style, while maintaining the oriental traditions, which may be beneficial to the establishment of an essential bioinformatic network of the Biobank, leading to possible biomedicine industry development, and, certainly, the exploration of critical issues related to ethnic, legal, and social issues of genomic medicine in Taiwan.

Application & review

The initiation of the whole plan has gone through a long policy decision and review process. Firstly, a scientific delegation was sent by the government to conduct a field study in the USA, UK, Iceland and Singapore. Then, the National Science Council, subject to the conclusion of independent peer review, granted Academia SINICA of Taiwan a research plan for a feasibility study [105]. The plan was aimed to simulate the scientific procedure for tissue sample collection and storage. Among variable issues pro-

posed for studies, the ELSI concern was placed at the top and a final report was officially released in November, 2007.

On the other hand, the Department of Health (DOH) also started its Pilot Research Plan in March, 2007 [106]. Again, Academia SINICA won the bid out of the public competition. In this 4-year term research plan, taking international development experiences into consideration, the goals set for the research are variable and extensive, including the substantiation of Biobank's scientific values, the examination of possible ELSI restraints, the design of required public communication and ethical/legal governance frameworks, the evaluation of future operation mechanism and their legal foundations, and, furthermore, the feasible industrial vision and benefit sharing. After completing its focal study on ELSI issues, the plan is heading into the second year work, which aims to develop an ethically sound procedure for tissue sample collection. Subject to the newly released 'Ethical Governance Framework' (draft), this plan converges with the former Feasibility Study and tries to lay a scientific and ethical foundation for further Taiwan Biobank development jointly.

Among all the review processes, in addition to the continuingly raised ELSI concerns, the methodology of recruitment has been kept questioned, too. Indeed, the application of voluntary enrollment by the Taiwan Biobank would certainly incur the questions regarding recruitment bias. However, it is arguable that while the risk of bias in voluntary participation may be higher than other random choice approaches, the sufficient amount of participants would be even more critical to the success of a biobank development. Indeed, the biobank by itself is not created for a single research purpose only. Rather, it aims to support the future variable type of studies. Therefore, the willingness of participant's enrollment and continuing support will be taken as the premise for the success of the project. Without this, the spirit of random choice may be in vain.

In other words, it might be reasonable for a case–controlled study to recruit on a random choice basis, as the researcher does not need to worry about the future application of these collected data. On the other hand, the biobank shall maintain the tissue and extracted information for further research purposes. The 'voluntariness' of a participant's general consent and long stay become critical. Anticipating the higher refusal ratio in participation in the biobanking recruitment, it becomes logical to proceed with the voluntary enrollment mode. Otherwise, the refusal ratio will definitely deteriorate the value of random choice.

Besides, it has been the basic principle of a cohort study that the tracking and analysis shall be conducted subject to the base materials collected since the very beginning, including the risk factors and biosample information. Therefore, there should be no doubt concerning the sample selection. However, it does prompt the question of whether these collected samples are adequate as a representation. Trying to overcome the problem, the research methodology has been enhanced to expand the coverage of weighting data for analysis, including the population, age, gender and so on. In addition, it is believable that the expansion of recruitment scope, distribution of the information to the society by large and the promotion of an effective public communication/consultation platform can be helpful in relieving the problem.

Funding

The whole plan is funded by the Taiwan government. For the Feasibility Study, a total budget of approximately US$680,000 was sponsored by the National Science Council. On the other hand, the Pilot Research is backed up by the DOH, with appropriated 4-year term funding of approximately US$14,000,000. For the first- and the second-year budget, the allocated fund has been approximately US$4,700,000. In the future, the operation cost of institutionalization will be further determined according to new legislation.

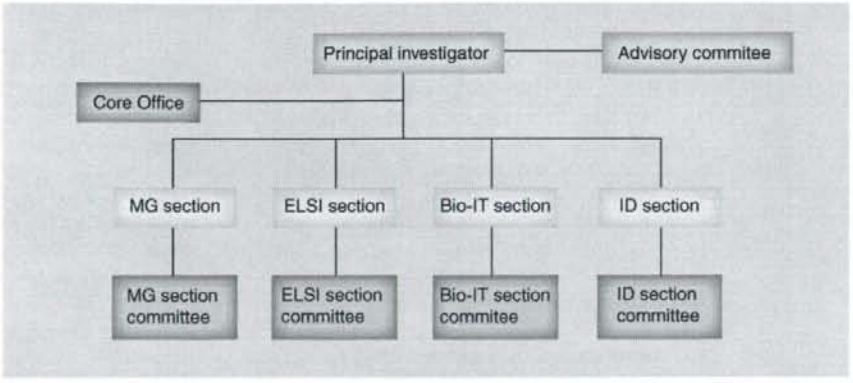
Methodology & participating

The Feasibility Study is, by nature, preliminary research. It cares more about the legitimacy of tissue sample collection and the storage process. On the other hand, the aim of the Pilot Research has been more comprehensive, trying to articulate a complete picture for Taiwan Biobank development. The Pilot Research Plan is made up of four sections:

- Medical Genetics (MG)
- ELSI
- Bio-Information Technology
- Industrial Development

The MG section is undertaken by the Institute of Biomedical Sciences, Academia SINICA, which refers to the methodology of the UK Biobank in research design. The Taiwan Biobank

Figure 1. Organization chart of the Taiwan Biobank.



Bio-IT: Bio-Information Technology; ELSI: Ethical, legal, social issues; ID: Industrial Development; MG: Medical Genetics.

research organization chart is illustrated in Figure 1.

As far as SINICA is concerned, the contemporary research experiences are mainly case–control studies in essence. The methodology tends to focus on the examination of previous experiences and can easily ignore the influence of the latent factors. Thus, errors may occur in the research findings. Now, the prospective cohort study proposed in conjunction with the Biobank development, aiming at the future multifactor studies, may provide evolving results retrievable in a lasting period of time. This is hoped to be helpful for future predictive and/or individualized medicine R&D.

However, this kind of research design can hardly provide a comprehensive investigative discovery without collecting enough samples for examination, and on a retrievable basis, which is costly and burdensome. This can partially explain why a well-planned biobank is necessary.

After carrying out a comparative study among different countries' approaches, the UK experience has been taken with preference by the MG section. Following the same logic, the recruitment plan was created as listed in the Participant Recruitment Plan of Figure 2.

Following this design, as mentioned above, the Taiwan Biobank plans to recruit up to 200,000 healthy participants aged between 30 and 70 years within the next 10 years. The project investigator of the SINICA will collect 33 ml venous blood and other samples mentioned above from participants at associated community hospitals, through the trained and selected study nurse, and subject to the ELSI governance framework approved by the Institutional Review Board (IRB). The collected samples and whatever information extracted from these will be, in compliance with the certified procedure provided by the ELSI section and contemporary research regulation regarding human tissue collection, stored in a secured facility or databank in trust of the general public and subject to a comprehensive legal and ethical governance framework created by law.

The ELSI section is undertaken by The Foundation of Medical Professionals Alliance, joined by the Graduate Institute of Philosophy, National Central University; Bioethics & Law Center, National Tsing Hua University; and the Social Empowerment Alliance. The ELSI section is responsible for various tasks concerning ELSI, including the articulation of the complete framework of ethical and legal governance, drafting and preparing the related documents and study of the corresponding legislation. Besides, one of the most important works for this section is the promotion of the public communication and trust.

The perfection of ESLI is considered to be the prerequisite of Taiwan Biobank development, the specific content of which will be further explained in detail later.

The Bio-Information Technology section is ran by the Institute for Information Industry. It is the mandate of the section to design an information system in compliance with the regulatory norms promulgated by the ELSI group and compatible with the specifications requested by the MG section.